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Role of TRIB3 pseudokinase in breast cancer development and progression

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INTRODUCTION

Breast cancer is the second cause of cancer death in women. About 85% of all breast tumors are hormone receptor-positive. The standard treatment in this type of tumors is the endocrine therapy, but there are about 20-30% of cases where the tumors became resistant to this therapy, frequently related with PI3k/AKT pathway activation. Thus, finding new biomarkers and therapeutic targets to overcome this treatment failure is crucial to increase patient survival.

Tribbles pseudokinase 3 (TRIB3) participates in the regulation of multiple signaling pathways that are involved in different cellular processes like cell survival, proliferation or migration. Emerging evidences obtained during the last few years suggest that TRIB3 is a crucial modulator of tumorigenesis. Recent observations by our research group have shown that TRIB3 plays a tumor suppressor role in several models of cancer through a mechanism that relies on the regulation of the PI3K/AKT axis.

Although there is limited and often conflicting literature concerning to the role of TRIB3 in breast cancer, the existing data suggest that this pseudokinase could be deregulated during the development of this pathology.

OBJECTIVES

Our main goal is to investigate the role of TRIB3 in the regulation of breast cancer progression and clarify the role played by this protein in different BC subtypes.

METODOLOGY

As a first approach to answer this question, we studied the effect of TRIB3 genetic inhibition on the survival, proliferation, migration and the degree of activation of the AKT pathway of breast cancer cell lines exhibiting different molecular features (BT474 (ER+ HER2+), AU565 (ER+ HER2+), 361 (ER+ HER2+), MCF7 (ER+ HER2-), T47D (ER+ HER2-), ZR75B (ER+ HER2-) or MDA-MB-231 (triple negative).

In addition, we analyzed the levels and subcellular location of TRIB3 in a Tissue microarray generated with samples obtained from 273 hormone receptor-positive breast cancer patients.

RESULTS

Our results show that TRIB3 genetic inactivation increases the proliferation and invasiveness of 361, AU565 and BT474 (ER+, HER2+) whereas it decreases both parameters in MCF7 and ZR75B (ER+, HER2-) cell lines. Our data also show that TRIB3 tumor suppressor activity correlates with its ability to negatively regulate the AKT/FOXO pathway in breast cancer cell lines.

Likewise, we found that higher TRIB3 levels correlated with a better prognosis and reduced metastasis in samples derived from ER-positive BC patients.

CONCLUSIONS

Our findings support the notion that TRIB3 may play a tumor suppressor role in hormone receptor-positive breast cancer via negative regulation of the PI3K/AKT/FOXO axis. However, we also found that TRIB3 could play an oncogenic role in certain BC cell lines. Our working hypothesis is that this dual role of TRIB3 is determined by the weight of the PI3K/AKT pathway as a driver alteration in BC progression.

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